Abstract. Aim: The feasibility and safety of a presurgical treatment approach with sunitinib for renal cell carcinoma (RCC) with level III/IV tumour thrombus in the inferior vena cava (IVC) were to be evaluated and its potential ability to reduce the surgical morbidity explored. Patients and Methods: In our institution, we treated five consecutive patients with suspected RCC and a level III/IV IVC tumour thrombus with preoperative sunitinib (50 mg, 4 weeks on, 2 weeks off). Side dose effects were assessed and the effect on the tumour size and the dependent surgical approach documented with a computed tomographic scan before and after the treatment. The data were analyzed retrospectively. Results: The overall tolerability to presurgical sunitinib was good. All procedures were carried out without perioperative complications. In four patients, a reduction in tumour size was observed, which resulted in avoidance of a bicavital surgical approach with cardiopulmonary bypass in one patient. This patient was diagnosed with papillary renal cancer; the other four patients had clear cell carcinomas. Conclusion: Presurgical treatment with sunitinib is able to ease surgery for RCC tumour thrombi regardless of the histological subtype in selected patients. In our series, surgery was possible without additional morbidity. Two courses of a presurgical therapy with sunitinib seems to be an appropriate duration. In accordance with previously published data, presurgical sunitinib treatment may become more widely used in RCC with level III/IV tumour thrombi but administered with restraint in cases of level I/III thrombi. The effects on the risk of recurrence and survival remain to be evaluated prospectively.

Renal cell carcinoma (RCC) has the ability to invade venous blood vessels. A tumour thrombus in the renal vein is observed in up to 10% of patients with newly diagnosed RCC (1). This vessel invasion can continue into the inferior vena cava (IVC) and may eventually extend to the level of the diaphragm and the right atrium. The surgical therapy of these advanced tumours is challenging and often requires a thoracoabdominal approach with sternotomy and optional cardiac arrest with extracorporeal circulation for better surgical control. Surgery for these tumors is always a high-risk procedure. Nevertheless, oncological long-term survival has been documented (2).

The advances in medical therapy of RCC achieved in the last few years have prolonged the progression-free survival of patients with metastatic disease. These improvements raise the question if a presurgical medical treatment for patients with advanced RCC may be beneficial, as more than half of these patients have subclinical metastases (3). The aims of this approach are various. Patients with progression during the presurgical treatment most likely are not candidates for cytoreductive nephrectomy (4). In responding patients, not only the clinical, but also the histological response can be evaluated, which may guide subsequent treatment decisions. Moreover, presurgical medical treatment has the potential to reduce the extent of surgical invasiveness: nephron-sparing surgery in patients with a single kidney or chronic kidney disease can be facilitated (5), a tumour thrombus in the vena cava reduced and the infiltration into adjacent organs lessoned, which may ease surgery and increase the likelihood of negative surgical margins. Concerning patients with an extended tumour thrombus, who this article focuses on, an additional intent of the presurgical treatment is avoiding a bicavital surgical procedure with cardiac arrest and thus reducing the perioperative morbidity and mortality. Lowering the upper level of the tumour thrombus speculatively improves disease-free survival, as it has been shown that a higher level of a tumour thrombus significantly correlates with a poorer prognosis.
Safety concerns such as wound-healing delays and perioperative bleeding may be raised discussing vascular endothelial growth factor (VEGF)-targeted presurgical therapy. In fact, some problems have been recorded, including an episode of intraoperative liver bleeding, and leakage of a bowel anastomosis, the latter seen after pre-treatment with bevacizumab (6). But larger series describe no difference compared to patients primarily operated on (7, 8).

Feasibility, safety and the implications for the surgical approach in a larger series of RCC patients with suprahepatic tumour thrombi had not been evaluated until recently, when Cost published retrospective data showing a reduction of the tumor thrombi in two out of four patients with level III/IV thrombi treated with sunitinib (9). Our series of five patients confirms these results.

**Patients and Methods**

Between June 2009 and October 2010, we treated five consecutive patients with RCC and a Clark level III/IV tumour thrombus of the IVC presurgically with sunitinib. All patients had given written informed consent prior to the first drug administration.

Patient 1 and 3 had a tumour thrombus extending into the right atrium at diagnosis (level IV), patient 2 at the lower border of the atrium (level III/IV) and the other two patients had thrombi over the level of the hepatic veins (level III). One therapy course included a period of four weeks of 50 mg of sunitinib daily and two weeks off treatment. Two courses of sunitinib therapy were administered to four patients with level III/IV thrombi treated with sunitinib (9). Our series of five patients confirms these results.

### Table I. Patient characteristics.

<table>
<thead>
<tr>
<th>No.</th>
<th>Thrombus level</th>
<th>Side-effects (grade)</th>
<th>Histology</th>
<th>Thrombus size Pre-therapy</th>
<th>Thrombus size Post-therapy</th>
<th>Change (craniocaudal) (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Atrial</td>
<td>Anorexia (II-III), gout, cheilitis, neutropenia (II), anemia (II)</td>
<td>Clear cell carcinoma cT3c, pN0 (0/10), cM1 (lung), G3</td>
<td>19×150 mm</td>
<td>15×135 mm</td>
<td>–10%</td>
</tr>
<tr>
<td>2</td>
<td>Atrial</td>
<td>Fatigue (II), tremor (II), (d/c 7 d prior), neutropenia+ anemia (II)</td>
<td>Papillary carcinoma cT3c, cN0, cM0, G3</td>
<td>35×112 mm</td>
<td>28×90 mm</td>
<td>–20%</td>
</tr>
<tr>
<td>3</td>
<td>Atrial</td>
<td>Epistaxis (II), mild anorexia</td>
<td>Poorly differentiated adenocarcinoma of the liver</td>
<td>17×130 mm</td>
<td>17×130 mm</td>
<td>0%</td>
</tr>
<tr>
<td>4</td>
<td>Hepatic veins</td>
<td>None</td>
<td>Clear cell carcinoma cT3b, pN0 (0/6), cM1 (lung), G3</td>
<td>40×69 mm</td>
<td>33×56 mm</td>
<td>–18.8%</td>
</tr>
<tr>
<td>5</td>
<td>Hepatic veins</td>
<td>Mucositis (III), weight loss (I), poor overall condition</td>
<td>Clear cell carcinoma cT3b, cN+ (pNx), cM1 (adrenal), cM1 (lung), G3</td>
<td>23×81 mm</td>
<td>16×60 mm</td>
<td>–26%</td>
</tr>
</tbody>
</table>

Safety concerns such as wound-healing delays and perioperative bleeding may be raised discussing vascular endothelial growth factor (VEGF)-targeted presurgical therapy. In fact, some problems have been recorded, including an episode of intraoperative liver bleeding, and leakage of a bowel anastomosis, the latter seen after pre-treatment with bevacizumab (6). But larger series describe no difference compared to patients primarily operated on (7, 8).

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### Results

The patient characteristics and key results, as well as the histopathological results, are summarized in Table I. All patients were able to complete the intended therapy, except patient 2, who discontinued the sunitinib treatment seven days early.

Patients 1 and 2 showed a tumour shrinkage in the post-sunitinib CT scan (–10%, 20% craniocaudally, see Figures 1 and 2). Patient 1 had a larger reduction of the thrombus diameter than its craniocaudal extension. A decision was made to discontinue the sunitinib treatment and to perform an interdisciplinary surgical approach including sternotomy and extracorporeal circulation. Three months later, the patient presented to our Outpatient Clinic with metastatic disease in the liver and the lungs.

Patients 2 had a reduction of both tumour thrombus diameter and craniocaudal extension. The thrombus ended below the level of the hepatic vein inflow (level II) and the decision was made for a surgical procedure with an
abdominal approach only which was carried out without perioperative complications. For this patient, a bicavital surgical approach was avoided by the presurgical treatment. Patient 3 showed no change in tumour size and was operated on in an interdisciplinary bicavital approach with cardiovascular arrest. Three months later, he was in an excellent performance status and CT scans showed no signs of residual tumour or metastatic spread.

Patient 4 showed minor tumour regression in the CT scan performed after two courses of sunitinib (overall -18% craniocaudally). This finding and the excellent tolerability to the medical therapy prompted the decision to administer a third course of sunitinib. Thereafter, surgery was performed without complications. Six weeks later, resection of the pulmonary nodule was performed without any complications.

Patient 5 showed a marked reduction of the primary tumour and the vena caval tumour thrombus extension (-26% craniocaudally). Regarding the metastatic spread the pulmonary nodules were unchanged, whereas the hepatic metastases had increased in size and number but appeared almost completely cystically reorganized. After surgery the tyrosine kinase inhibitor type was changed to pazopanib because of the observed side-effects with sunitinib.

In summary, the presurgical sunitinib treatment was able to reduce the tumour burden in four out of five patients and helped to avoid a bicavital approach with sternotomy in one patient (patient 2). For three patients, surgery was facilitated due to reduction of the tumour thrombus diameter. Nevertheless, this facilitation of surgery with reduced tumor extension is hard to objectify.

All procedures were carried out without any major perioperative complications or wound-healing disturbances. As the observed tumour shrinkage may simply have been due to a reduction of an appositional blood clot by the simultaneously administered therapeutic anticoagulants, the tumour thrombus was examined in all patients. All patients had a tumour thrombus established by malignant cells.

Discussion

There is continuously growing interest in neoadjuvant and presurgical treatment strategies in RCC. Mostly sunitinib and sorafenib have been used for this purpose. An overview of the studies conducted therefore is given in Table II.

There are some case reports and case series of presurgical treatment modalities in RCC which state that nephrectomy is feasible without an increase in perioperative morbidity and mortality (7, 8) and that surgery can be eased (12), nephron-sparing surgery enabled (5, 13) or cases with widely advanced metastases can be reconsidered for cytoreductive nephrectomy (12). Overall, a response to preoperative tyrosine kinase inhibitors has been shown to be possible in primary tumours (10, 14, 15), venous thrombi (16-20), local
tumour recurrence in the renal fossa (15) local lymph nodes (15, 21) and distant metastases (14).

Surgically managed patients with an atrial tumour thrombus have been shown to have a better overall survival in comparison to non-surgical patients (1). Concerning atrial tumour thrombi, there are three described cases in the literature so far in which two cycles of presurgical sunitinib achieved avoidance of a sternotomy (16, 17). In addition, there is one described histologically complete remission of an RCC with an IVC tumour thrombus from six months of sunitinib treatment (18). Other case reports illustrate patients with vena cava tumour thrombi in whom the use of presurgical sunitinib enabled the performance of a laparoscopic nephrectomy (19) and reduced a vena cava thrombus to a renal vein thrombus (20). All these data need to be handled with care bearing in mind a possible publication bias. Recently, Cost et al. published retrospective data about 25 patients with RCC and a tumour thrombus level at II-IV who received preoperative medical treatment with different medications. Only three patients demonstrated a reduction in the thrombus level, all of whom were treated with sunitinib. This study included four patients with a level III/IV tumour thrombus treated with sunitinib, two of whom responded (level IV to level III, level III to level II, respectively) (9).

In our consecutive series of five patients, two cycles of therapy with sunitinib were empirically administered (three courses in one patient). The timing of side-effects beginning mid-second cycle in two patients and the observed response in our patients make the treatment duration of two cycles seem an appropriate compromise between the necessity for a definitive therapy in the face of a life-threatening disease with the imminent risk of a devastating embolism, the toxicity of the medication and the need for down-staging. This is consistent with the presented literature. Moreover, it has been shown that the maximum size reduction induced by sunitinib occurs after two to three months of therapy (10).

Figure 2. Patient 2. The extension of the tumour before therapy (level III/IV) is shown on the left side and after therapy on the right side. There was a distinct reduction in tumour thrombus size, such that surgery could be performed without cardiovascular arrest and a thoracic approach. Top: Reduced dimension of the thrombus: in the left image it reaches the ventricular level (arrow), in the right, there is no thrombus visible at the hepatic vein inflow (level II). Bottom: Reduction of thrombus volume.
In our series, the presurgical treatment was safely administered. First of all, we did not see any complications from thrombus or blood clot embolisation into the lungs. In some of these locally advanced cases, presurgical medical therapy may achieve avoidance of a sternotomy, as we saw in one of the five patients and has been shown before in some case reports (see above). Whether other patients that need a major surgical procedure with extracorporeal circulation also benefit from the medical therapy is difficult to determine. The reduced diameter we observed in three cases makes the thrombus better accessible for surgery, but this ease of surgery is highly subjective.

As it was shown that tumour thrombi of level III/IV in comparison with those of level I/II confer an unfavourable long-term outcome and higher rate of recurrence (22) this may also be true for patients with a reduction of the cranio-caudal extension of the thrombus by a presurgical therapy. The proven correlation between the extent of the tumour thrombus in the vena cava and the frequency of tumour recurrence can be an argument for a medical pretreatment in patients with advanced thrombi.

Whether the timing of surgery affects the prognosis of the patients will be addressed in a randomized, phase III study conducted by the European Organization for
Research and Treatment of Cancer EORTC (SURTIME, EORTC 30073) (23). A total of 458 patients will be randomized to either upfront nephrectomy with adjuvant sunitinib or three months of preoperative sunitinib followed by surgery. This study will not be limited to tumour thrombi of the vena cava.

Although many of the cited studies describe tumour shrinkage during preoperative sunitinib treatment, one study describes two patients with IVC tumour thrombi from RCC which continued to grow despite Sunitinib (24). These conflicting results need to be taken into consideration when counselling and selecting patients for presurgical medical treatment.

An advantage of the preoperative regimen is the knowledge of the histopathological and clinical reponse of the tumour to sunitinib, which may influence the choice of agent in a situation of tumour recurrence or progression. In cases lacking a tumour response, a therapeutic switch can be accelerated.

An unexpected aspect is that the single patient in our series in whom a bivacital approach was avoided had a papillary RCC. In this context the role of a pre-treatment biopsy needs to be discussed. As there is emerging data showing a poorer response of non-clear cell histology renal cancer to VEGF-targeted tyrosine kinase inhibitor treatment (J Clin Oncol 28: 15s, 2010 (suppl; abstr 4604)), a biopsy should be performed to guide the therapeutic decisions. Additionally, information about the histological and molecular phenotype before the medical intervention can also then be obtained. As the patients included in this article were started on the medication when the available evidence suggested effectiveness of sunitinib in non-clear cell renal cancer (25), we did not perform a biopsy.

In conclusion, we deem two cycles of presurgical sunitinib treatment a considerable treatment option in patients with a level III/IV IVC tumour thrombus from RCC, at least for patients with a high likelihood of extremely difficult surgery. It may help to ease surgery and, at least in our series, was performed without additional harm to the patient. Nevertheless, we know that only one-third of all patients respond to sunitinib treatment; for the others, surgery is delayed by the presurgical treatment (26). As mentioned, there are reports about thrombi continuing to grow during medical pretreatment in the literature, hence patients must be counselled carefully.

Our data is biased by its retrospective acquisition and the results should be validated in a prospective manner, although this will be hard to conduct due to the paucity of cases (27-30).

**Conflict of Interest**

None.

**References**


